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EXAMINER	
ART UNIT	PAPER NUMBER
1615	5

DATE MAILED: 03/05/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 6/6/95 and 8/4/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-5, 8-17 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 6, 7 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1-5, 8-17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☑ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☑ been received ☐ not been received ☐ been filed in parent application, serial no. 07/768,858; filed on 10/10/90.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

15. The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1816.

16. Applicant is reminded that affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application.

17. Claims 6-7 have been cancelled.
Claims 1-5 and 8-17 are pending and being acted upon.

18. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

19. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

20. The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

21. Claims 1-5 and 8-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18-19 and 30-36 of copending application Serial No. 08/289,532. Although the conflicting claims are not identical, they are not patentably distinct from each other because both applications are drawn essentially to the same use of CD4- and/or CD8-specific antibodies in the generation of immunological tolerance. Therefore

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

22. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

23. The specification is objected to and claims 1-5 and 8-17 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

Applicant has not disclosed how to use non-depleting CD4 and/or CD8 monoclonal antibodies with or without depleting CD4 and/or CD8 monoclonal antibodies as therapeutic agents to induce tolerance to the claimed broad range of antigens in all species including humans. There is insufficient information or nexus with respect to the scope of the claimed methods to use applicant's invention for the following reasons.

The instant disclosure provides evidence that non-depleting antibodies have been able to induce some tolerance for some antigens in certain well-defined murine experimental systems (e.g. across minor MHC barriers in mice); including how to induce tolerance for human and rat gamma globulins, skin grafts and bone marrow grafts in particular mouse strain combinations. However, it is not clear from the specification whether non-depleting antibodies alone or in combination with depleting antibodies can generate tolerance to all antigens or across all MHC barriers, in all species and, in particular, for transplantation antigens, autoantigens and immunoglobulins in humans as the intended invention.

In vitro assays and in vivo animal studies do not necessarily correlate with in vivo human efficacy. Since the therapeutic indices of immunosuppressive antibodies can be species- and model-dependent, it is not clear that reliance on the in vitro and in vivo experimental murine models accurately reflects the relative efficacy of the claimed therapeutic products and methods for the induction of tolerance.

Although the applicant has exemplified some success with the instant methods and compositions for tolerance induction for certain antigens in certain mouse strain combinations with non-immunogenic rat antibodies, there is insufficient evidence or nexus that such therapy would work for any antigen system or in larger animals including humans, encompassed by the claims and the intent of the invention. The standards of enablement that are commensurate in scope with the instant invention would be the induction of tolerance across weak and strong antigenic barriers in human therapy. Therefore, applicant's evidence of particular murine examples of tolerance induction across weak antigenic barriers presented in the application would not be predictive for the successful induction of tolerance to the scope of antigens in larger animals, including humans.

Pharmaceutical therapies are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has not effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. In vitro and animal model studies have not correlated well with in vivo clinical trial results in humans. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Concerning antibody therapy, Harris et al. states that there is widespread acceptance that there is little future for the use of rodent monoclonal antibodies for in vivo human therapy (page 42, column 2) and that repeated dosing with chimeric antibodies is ineffective due to residual anti-idiotypic responses (page 42, column 3) (Tibtech, 1993; 892 of record). Humanized antibodies present serious problems with immunogenicity, since the idiotype of such antibodies will contain unique amino acid sequences.

Charlton et al. teach that tolerance to aggregated human IgG but not ovalbumin can be induced by concurrent administration of depleting or non-depleting anti-L3T4 (anti-CD4) monoclonal

antibodies (see entire document, particularly page 4, Figures 2 and 3)(Immunol. Cell Biol., 1989; 1449, AS). In their discussion of their work on the induction of immune tolerance by non-depleting anti-L3T4 monoclonal antibodies, Carteron et al. cites previous studies which have shown that anti-L3T4 (anti-CD4) depletes L3T4 cells in vivo induces tolerance to certain antigens including 2C7, HGG (human gamma globulin), several antibodies that do not bind cells and pancreatic islet cell grafts (page 715, column 2, lines 21-36)(J. Immunol., 1989; 1449, AR). However, tolerance therapy with intact anti-L3T4(CD4) antibody fails to permit tolerance to chicken gamma-globulin, keyhole limpet hemocyanin or to various monoclonal antibodies that bind cells. Therefore effective immunological tolerance induction by non-depleting antibodies as well as depleting antibodies depends on the antigen. Also, the specification exemplifies that not all mouse strain combinations work in the same manner (e.g. specification; page 33, lines 1-14) and that each mouse in a successful mouse strain combination is tolerizable (e.g. specification; page 30, lines 1-20). The applicant states that "this difference in behavior of the strain combinations is compatible with that seen in naive mice and probably lies in the complex pattern of shared and unique minor antigens" (page 33, lines 9-13).

Concerning the efficacy of CD4-specific antibodies in immunosuppression, Russell et al. disclose that CD4-specific antibodies have had varying success as an immunosuppressive reagents (BMJ, 1992; see entire document, particularly, page 305, column 1, paragraph 3; 892, of record). Even long term transplant recipients require long term maintenance immunosuppression.

Concerning the complexity of tolerance induction whether one is relying on the particular targeted antigen system or the particular responsible host immune compartment; applicant is directed to the review on immunological tolerance by Nossal that addresses the differences between the tolerogenicity of different antigens and the multiple immunological pathways that are operating (Fundamental Immunol., 1989; 892 of record). Furthermore, Nossal discloses that therapeutic implications are hampered by the multiepitopic nature of many diseases and the real-life situation of a host's previous exposure to antigen (see pages 581-583). Also, Nossal discloses that CD4-specific antibody did confer specific unresponsiveness to a particular protein antigen, this was not the case with a pancreatic islet allograft (see page 582, column 2, paragraph 1).

As acknowledged in the art and by applicant's publications, it is clear that the antibody requirement for tolerance induction varies according to the immunological challenge. Watson et al.

(J. Surg., 1993; 892 of record) clearly states that tolerance induction in rodent is relatively easy to achieve and that promising tolerogenic therapies need to be developed in large animal models before being considered for clinical application (see Introduction and Discussion). Here, CD4 or CD8 antibodies alone did not alter the tempo of renal allograft rejection in spite of evidence that adequate monoclonal antibody levels were achieved in dogs (Discussion). Although there was some prolongation of allograft survival with some combination therapy, a much longer survival would be required to indicate tolerance. Also, it is noted that therapy was stopped prematurely following adverse reactions associated with the host response to antibody administration.

Watson et al. (Tissue Antigens, 1994) clearly express the barriers of extrapolating tolerance as well as immunosuppression from rodents to large animals or human subjects (entire document, particularly the Introduction and Discussion).

Watson et al. (Transplant. Proc., 1995) similarly address differences in tolerogenic regimens between rodents and large animals including man (see entire document). Here, it is noted that prolonged antibody treatment was not possible and that other immunosuppressive agents were required for extending antibody administration. However, tolerance induction was still not achieved.

Chen et al. disclose that the instant CD4/CD8-specific antibody-mediated blocking protocol failed to generate tolerance in a model of xenogeneic skin grafts even though this protocol worked in other murine tolerance models (Transplant. Proc., 1994; 892, of record), as disclosed in the specification. Even applicant's specification discloses that complete tolerance in certain strain combinations across certain antigenic barriers could not be accomplished (for example, see pages 28-29).

Therefore it is clear that art including the inventive entity would not predict the ability or the efficacy of tolerogenic regimens based upon a few experimental murine models. Furthermore, it is clear that prolonged use of antibody regimens for the induction of tolerance depends on the administration of other immunosuppressive regimens; therefore antibodies in the absence of such immunosuppressive agents would be even less likely to lead to immunological tolerance.

The specification does not adequately teach how to effectively achieve immunological tolerance in any mammal including humans, other than a few murine experimental models, by administering non-depleting CD4/CD8-specific antibodies with/without other immunosuppressive agents. The specification

does not teach how to extrapolate data obtained from in vitro inhibition assays or in vivo experimental murine models to the development of effective in vivo tolerogenic therapeutic regimens, commensurate in scope with the claimed invention. Therefore, the skilled artisan could not predict the efficacy of the claimed methods relying upon non-depleting antibodies exemplified in the specification, encompassed by the claims.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective induction of immunological tolerance, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods and products are effective for establishing immunological tolerance, commensurate in scope with the claimed invention.

24. Claims 1-5 and 8-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-5 and 8-17 are indefinite in the recitation of "CD4 monoclonal antibody" or "CD8 monoclonal antibody" because the appropriate designation is "CD4 specific monoclonal antibody" or "CD8 specific monoclonal antibody".

B) Claims 10 and 11 are indefinite in the recitation of "pack" because its characteristics are not known. Amendment should replace this word with "kit".

C) Claims 15 and 17 are indefinite in the recitation of " to an antigen it is wished to administer thereto" because the parameters of this phrase are unknown.

D) Claim 16 is indefinite in the recitation of "antigen already possessed by the subject" because it is unclear what are the characteristics of this phrase. Amendment should replace this phrase with "autoantigens".

The amendments must be supported by the specification so as not to add any new matter.

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

27. Claims 3-5 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Waldmann. (Ann. Rev. Immunol., see entire document, in particular pages 425-432; 1449, #AT). Waldmann teaches "tolerance therapy" to certain protein antigens and transplantation antigens with CD4 and CD8 specific antibodies. The reference teaches non-depleting CD4 specific antibodies can induce immunological tolerance to rat and human gamma globulins. Also, transplantation tolerance including bone marrow and skin can be achieved through the combination of CD4 and CD8 specific antibody therapy. Non-depleting CD8 specific antibody could lead to tolerance if CD4 cells were deleted with depleting CD4 specific antibody.

A composition is a composition irrespective of what its intended use is. See In re Tuominen, 213 USPQ 89 (CCPA 1982).

28. Claims 3 and 5 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Qin et al. (J. Exp. Med. 1989; 1449, #AS).

Qin et al. teach the induction of tolerance with non-depleting CD4-specific antibodies in combination with depleting CD8-specific antibodies and bone marrow (see page 785, Table IV). Depleting CD8-specific antibody is an immunosuppressive agent.

29. Claims 1-5 and 8-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Qin et al. (J. Exp. Med., 1989; 1449, #AS) in view of Waldmann (Ann. Rev. Immunol., 1989; 1449, #AT), Waldmann (Am. J. Kid. Dis., 1988; 892, of record) and Cateron et al. (J. Immunol., 1988; 1449, AR). The instant claims are drawn to the use of the combination of non-depleting CD4- and CD8-specific antibodies to induce immunological tolerance; and in addition, are drawn to use of such non-depleting antibodies in combination with CD4 and/or CD8 depleting antibodies to induce such tolerance.

Qin et al. teach the use of CD4- and CD8-specific monoclonal antibody therapy including the combination of non-depleting and depleting antibodies to induce transplantation tolerance (see entire document). Qin et al. teach that both recipient CD4 and CD8 T cell subsets are independently capable of resisting donor bone marrow grafts and that both had to be controlled to ensure transplantation tolerance. The CD8 subset can be controlled by the use of non-depleting rat IgG2b $F(ab')_2$ CD8-specific antibody fragments or non-depleting rat IgG2a CD8-specific antibodies (pages 784-785, Table IV). Also, tolerance induction can be accomplished with a non-depleting rat IgG2a CD4-specific monoclonal antibody in combination with a depleting rat IgG2b CD8-specific monoclonal antibody (pages 784-785, Table IV). Qin et al. do not exemplify that the combination of nondepleting CD4- and CD8-specific rat IgG2a monoclonal antibodies leads to tolerance, however tolerance does occur when either monoclonal antibody is combined with the complementary depleting rat IgG2a monoclonal antibodies. The instant application using the same mouse strain combination exemplifies the successful induction of tolerance with non-depleting CD4- and CD8-specific antibodies (specification, page 22, lines 4-25). This discrepancy between the reference and the instant application on the same model of transplantation tolerance could be due to amount of antibody therapy and the duration of this therapy. For example, Qin et al. teach the use of 0.5 mg total antibody/day for 15 days (page 785, Table IV). In the instant application, the treatment included 2 mg total antibody/day for three weeks. Qin et al. suggest that the failure of non-depleting $F(ab')_2$ CD4-specific antibodies to induce tolerance could be simply an issue of sufficient quantity (page 791, lines 22-24). Qin et al. also teach that functional anergy and not clonal deletion contribute to the unresponsiveness in CBA/Ca (Mls^b) mice to AKR/J (Mls^a) antigens after antibody therapy (pages 785-790). Therefore, Qin et al. teach that both mature CD4 and CD8 cells are tolerizable without depletion (page 791, lines 26-28). Qin et al. also teach that for strong histocompatibility differences, the use of additional monoclonal antibodies or irradiation can be used in addition to the CD4/CD8 antibody protocol (page 792, lines 13-17). Qin et al. do not teach the CD4/CD8 antibody protocol for

inducing tolerance in "an antigen already possessed by the subject" such as an autoantigen.

Carteron et al. teach the ability of CD4(L3T4)-specific antibodies to induce immune tolerance is independent of its ability to deplete CD4(L3T4) cells (see entire document). In further support of antibody quantity at issue, it is noted that Carteron et al. employed 1 mg antibody treatment every other day for 18 days. Therefore, the ability of inducing tolerance without cell depletion was shown to occur against some antigens, if sufficient antibody treatment was provided.

Therefore, it was apparent to the ordinary artisan at the time the invention was made that the ability to induce tolerance was related to the quantity of antibody and the nature of a particular antibody (i.e. one CD4-specific antibody versus another CD4-specific antibody).

Waldmann (Ann. Rev. Immunol.) teaches CD4/CD8 antibody therapy will lead to other rational tolerance therapies using monoclonal antibodies together with other immunosuppressive drugs (page 428, lines 3-8). Waldmann teaches the importance of CD4 therapy in autoimmunity including the use of non-depleting $F(ab')_2$ fragments of CD4 monoclonal antibodies (pages 423-425). Waldmann further teaches that it was known in the art that the improved therapeutic effect of short-term therapy with both CD4- and CD8-specific antibodies compared to CD4 antibody alone in diabetes that develops following low dose steptozotocin or experimental thyroiditis (page 424, lines 30-36), as reported by Kantwerk et al. (Clin. Exp. Immunol. 70: 585, 1987) and Kong et al. (Immunobiology (Suppl.) 3: 30, 1987).

Waldmann (Am. J. Kid. Dis.) similarly teach that CD4-specific antibodies could induce the tolerance for certain antigens without cell ablation (see page 156, Antibodies Affecting T cell Function). Here, it is taught that CD4- and CD8-specific antibodies in conjunction with bone marrow cells (e.g. a source of antigen) could lead to tolerance.

One of ordinary skill in the art at the time the invention was made would have been motivated to induce immunological tolerance for therapeutic purposes such as transplantation tolerance and autoimmunity as well as tolerance induction to therapeutic murine antibodies themselves. Therefore, transplantation antigens, autoantigens and immunoglobulins would have all been targeted for tolerance at the time the invention was made. Antibody therapy has been effective for short-term use but not for long-term needs. It was well known in the art that one of the problems with antibody therapy is the development of the anti-murine antibody responses in patients. The ability of

CD4/CD8 therapy to induce specific unresponsiveness to murine gamma globulins and in transplantation provides great impetus to practice these tolerance therapies with CD4/CD8-specific monoclonal antibodies. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references to use non-depleting CD4 and CD8 monoclonal antibodies to induce tolerance to proteins, autoantigens and transplantation antigens.

In addition, protocols based on the use of combining non-depleting and depleting CD4/CD8 antibodies in various combinations as claimed would have been obvious to the ordinary artisan who would have selected the appropriate combination or protocol for the desired antigen to be tolerized. Such protocols would have been tailored to the immunogenicity of the targeted antigen(s). The routineer would have selected such combinations to achieve an operationally immature immune system as the appropriate environment to induce tolerance. For example, it would have been obvious to use depleting antibodies prior to non-depleting antibodies in certain cases in an effort to lessen the immunological challenge to tolerance induction, that is, it would be easier to tolerize a percentage rather than the sum total of the host's immunocompetent cells. Therefore, the claimed methods would have been obvious to one of ordinary skill in the art at the time the invention was made.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention, at least across weak antigenic systems. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

30. No claim is allowed.

31. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4065 or (703) 305-7939.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel
Patent Examiner
Group 1800
March 4, 1996